510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
DEVICE ONLY TEMPLATE

A. 510(k) Number:
k041720

B. Purpose for Submission:
New device

C. Analyte:
LDL Cholesterol

D. Type of Test:
Quantitative

E. Applicant:
Ortho-Clinical Diagnostics, Inc.

F. Proprietary and Established Names:
VITROS Chemistry Products dLDL Reagent
VITROS Chemistry Products Calibrator Kit 19
VITROS Chemistry Products FS Calibrator 1
VITROS Chemistry Products Performance Verifiers I and II

G. Regulatory Information:

1. Regulation section:
   862.1475, Lipoprotein Test System
   862.1150, Calibrator, Secondary
   862.1660, Single (specified) analyte controls (assayed and unassayed)

2. Classification:
   Class II

3. Product Code:
   MRR, JIT, JJX

4. Panel:
   75 - Chemistry

H. Intended Use:

1. Intended use(s):
   See Indications for Use below

2. Indication(s) for use:
   For *in vitro* diagnostic use only. VITROS Chemistry Products dLDL Reagent is used to quantitatively measure LDL Cholesterol (LDLC) concentration in serum and plasma. Low Density Lipoprotein (LDL) cholesterol is used to evaluate the risk of developing coronary heart disease (CHD). The risk of CHD increases with higher LDL cholesterol concentrations.

   For *in vitro* diagnostic use only. VITROS Chemistry Products Calibrator Kit 19 is used in conjunction with VITROS FS Calibrator 1 to calibrate VITROS 5,1 FS Chemistry Systems for the quantitative measurement of HDL and LDL cholesterol using VITROS dHDL and dLDL Reagents.

   For *in vitro* diagnostic use only. VITROS Chemistry Products Performance Verifiers I and II are assayed controls used to monitor performance on VITROS Chemistry Systems.

3. Special condition for use statement(s):
   Prescription Use only

4. Special instrument Requirements:
   Vitro 5,1 FS Chemistry System

I. Device Description:

The VITROS dLDL Reagent is a dual chambered package containing stable, ready-to-use liquid reagents that are used in a two-step reaction to quantitatively measure LDLC. VITROS Chemistry Products Calibrator Kit 19 is composed of a human serum based matrix spiked with high density lipoprotein and low density lipoprotein cholesterol and a stabilizer. VITROS Chemistry Products FS Calibrator 1 is composed of processed water and 0.9 % w/v sodium chloride. VITROS Performance Verifiers contain two levels of assayed controls and are prepared from processed human serum to which enzymes, electrolytes, stabilizers, preservatives, and other organic analytes have been added.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   Polymedco Lipi+Plus Direct LDL

2. Predicate K number(s):
   k020852

3. Comparison with predicate:

Similarities		
Item	**Device**	**Predicate**
Specimen pre-treatment	None required – homogenous assay	Same
Basic principle	Elimination enzymatic test	Same
Reagents	Liquid, ready to use	Same
Differences		
Item	**Device**	**Predicate**
Sample type	Serum and heparin plasma	Serum and heparin and EDTA plasma
Instrumentation	VITROS 5,1 FS Chemistry System	Dade Dimension
Reportable range	30-350 mg/dL	0-1000 mg/dL

K. Standard/Guidance Document Referenced (if applicable):

NCCLS EP6-A, NCCLS EP7-A, NCCLS EP9-A2, National Cholesterol Education Program Adult Treatment Panel III (ATP III)

L. Test Principle:

The VITROS dLDL Reagent is a dual chambered package containing stable, ready-to-use liquid reagents that are used in a two-step reaction. In the first step, with the addition of Reagent 1 (R1), non-LDL cholesterol (such as HDL, VLDL and Chylomicrons) is selectively eliminated by reaction with cholesterol esterase and cholesterol oxidase to form cholestenone and hydrogen peroxide. The peroxide generated is immediately scavenged by catalase. Addition of Reagent 2 (R2) initiates the second step, in which catalase is immediately inactivated with sodium azide. Surfactants then aid in dissociation of cholesterol and cholesterol esters from LDL particles and promote reaction with cholesterol esterase and cholesterol oxidase. The peroxide byproduct reacts with N-Ethyl-N-(2-hydroxy-3-sulfopropyl)-3-methylaniline (TOOS) and 4-aminoantipyrine in the presence of peroxidase to form a colored quinone dye, which is measured spectrophotometrically at 600 nm. Once a calibration has been performed for each reagent lot, the LDLC concentration in each unknown sample can be determined using the stored calibration curve and the measured absorbance obtained in the assay of the sample.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:
   - *a. Precision/Reproducibility:*

     Quality control materials were analyzed by ANOVA according to the method given in NCCLS EP5-A. A nested ANOVA was performed to estimate within-run, run-to-run (with-in day), day-to-day, week-to-week (cal-to-cal), and total with-in lab precision. Another nested ANOVA was performed to estimate with-in day, day-to-day, week-to-week (cal-to-cal) and total with-in lab precision.

The ANOVA results represent an approximation of the total, within-laboratory variability that would be observed using a single lot of reagents. The within-run, run-to-run, day-to-day, week-to-week, and total with-in lab precision results generated by the first nested ANOVA are summarized in Table 1. The results from the second nested ANOVA for with-in day, day-to-day, week-to-week, and total with-in lab are summarized in Table 2. Four calibration events were performed throughout the study, at one-week intervals. Within-run precision was determined using two-runs/ day with two replications per run. Within-Lab precision was determined using a single lot of reagents and calibrating weekly (4 calibration events). Within Day precision was determined using two-runs/ day with two replications per run.

Table 1 Precision Results from ANOVA #1

Conventional Units (mg/dL)								
Mean Conc.	**Within -run**	**Run-run**	**Day-day**	**Week-week**	**Total within-lab**	**Within-Lab CV%**	**No. Days**	**No. Observ.**
84.09	1.11	0.92	0.87	0.81	1.87	2.22	26	97
143.11	1.65	2.22	2.62	3.25	5.01	3.50	26	98

Table 2 Precision Results from ANOVA #2

Conventional Units (mg/dL)							
Mean Conc.	**Within-day**	**Day-day**	**Week-week**	**Total within-lab**	**Within-Lab CV%**	**No. Days**	**No. Observ.**
84.09	1.33	1.04	0.81	1.87	2.22	26	97
143.11	2.42	2.94	3.25	5.01	3.50	26	98

b. Linearity/assay reportable range:

A high pool was created by spiking a normal patient serum with a concentrate of human LDLC to achieve an estimated concentration of 550 mg/dL. The high pool was diluted with saline to create 12 further pools, for a total of 14 evaluation fluids. Five determinations of each of the 14 evaluation fluids were made, together with 6 determinations of VITROS Chemistry Products Performance Verifiers I and II. This experiment was performed three times, once with each of three lots on the VITROS system. The VITROS Systems were operated within normal conditions and were calibrated for the appropriate lot. Analysis by linear regression indicated that the assay is linear across the range 21- 402 mg/dL for all three lots tested. The data support a reportable range claim of 30-350 mg/dL. In addition, recovery studies were performed by diluting three serum and two plasma samples 1:2 with saline and measuring LDLC using three different lot numbers of reagent. The average mean % recovery

value across the three reagent lots was 103.2 % with an individual sample recovery range of 97.9 % to 108.0 %. The undiluted values of the five samples ranged from 246 mg/dL to 330 mg/dL. The dilution of patient samples with saline was determined to be acceptable up to a 1:2 dilution.

c. *Traceability (controls, calibrators, or method):*
Values assigned to the VITROS Chemistry Products Calibrator Kit 19 and VITROS Chemistry Products FS Calibrator Kit 1 for low-density lipoprotein cholesterol are traceable to the NIH/NCEP LDL Cholesterol Reference Method as calibrated with the HECTEF (Healthcare Technology Foundation, Japan) Certified Reference Material for Measurement of Total Cholesterol in Human Serum, JCCRM 211-1.

d. *Detection limit:*
The Lower Limit of Detection (LLD) is defined as the concentration that can be distinguished from zero using a predetermined confidence interval. The Lower Limit of Detection of the VITROS Chemistry Products dLDL Reagent assay is 0.27 mg/dL. The study details are provided below. Since 0.27 mg/ dL is not clinically relevant for the LDL assay, the low end of the reportable range was determined conservatively by using the linearity study data. Linearity was verified over a range of the assay for serum of 21-402 mg/dL LDLC. The data support a reportable range claim of 30-350 mg/dL LDLC.

e. *Analytical specificity:*
The effect of triglyceride concentration on the VITROS Chemistry Products dLDL assay was assessed by plotting the percent bias observed between the mean result obtained with the VITROS method and the predicate method (Lipi+Plus method on the Dade Dimension). The percent bias was plotted for 186 samples versus patient sample triglyceride concentration as determined using the VITROS Chemistry Products TRIG assay. A linear regression of the data shows that no significant correlation to bias exists for triglyceride concentration up to ~750 mg/dL. Interference studies for triglyceride were also conducted using Intralipid. 20% Intralipid and/or water was added to two human serum pools of different LDLC concentrations to prepare samples with 0 mg/dL (control pool), 250 mg/dL, 500 mg/dL, 650 mg/dL, 800 mg/dL and 1000 mg/dL Intralipid. Results were obtained on three reagent lots for each sample plotted with specificity limits, as defined in the design input, for both the high and low LDLC serum pool. A third order polynomial regression through the data in each plot indicates that samples containing Intralipid up to ~750 mg/dL meet specificity

limits. The substances listed in the table below were tested at LDLC nominal concentrations of approximately 115 mg/dL and found not to interfere, bias < 10 mg/dL (0.26 mmol/L), at the concentrations shown.

Compound	Concentration	
Acetaminophen	200 mg/L	1.3 mmol/L
Acetylsalicylic acid	500 mg/L	2.8 mmol/L
Allopurinol	10 mg/L	74 µmol/L
Ampicillin	600 mg/L	1.7 mmol/L
Ascorbic acid	3 mg/dL	0.17 mmol/L
Bilirubin	60 mg/dL	1.03 mmol/L
Carbamazepine	20 mg/L	85 µmol/L
Chloramphenicol	20 mg/L	62 µmol/L
Chlordiazepoxide	20 mg/L	60 µmol/L
Doxepine	10 mg/L	32 µmol/L
D-Penicillamine	55 mg/L	370 µmol/L
Erythromycin	400 mg/L	545 µmol/L
Furosemide	30 mg/L	91 µmol/L
Gentamicin	20 mg/L	42 µmol/L
Hemoglobin	1000 mg/dL	10 g/L
Methotrexate	0.45 mg/L	1 µmol/L
Phenobarbital	150 mg/L	646 µmol/L
Tetracycline	40 mg/L	90 µmol/L
Tolbutamide	300 mg/L	1.1 mmol/L
Valproic acid	300 mg/L	2.1 mmol/L

f. Assay cut-off:
Not applicable

2. Comparison studies:

a. Method comparison with predicate device:
Accuracy was evaluated based on NCCLS Protocol EP9-A2. The data below show the results of a comparison of samples analyzed on the VITROS 5,1 FS Chemistry System with those analyzed on a commercially available system.

Method Comparison for dLDL: Serum

				Conventional Units (mg/dL)			SI Units (mmol/L)		
	n	Slope	Correlation Coefficient	Range of Sample Conc.	Intercept	Sy.x	Range of Sample Conc.	Intercept	Sy.x
5,1 FS System vs. comparative method	165	1.03	0.991	41–300	-3.81	6.12	1.06–7.76	-0.099	0.16

b. Matrix comparison:
Sample types recommended are serum and heparin plasma. Fifty matched serum and Li-heparin plasma patient samples were tested. The bias between the mean value (n = 3) for each serum and plasma sample was calculated. Bias values were plotted against the specificity design goals for VITROS Chemistry Products dLDL assay (predetermined acceptance criteria) and fell within predetermined specificity limits.

3. Clinical studies:
   a. Clinical sensitivity:
   Not applicable
   b. Clinical specificity:
   Not applicable
   c. Other clinical supportive data (when a and b are not applicable):

4. Clinical cut-off:
   Not applicable

5. Expected values/Reference range:

   The reference Interval for LDLC is based on the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III); Executive Summary. NIH Publication No. 01-3670, National Institutes of Health. Bethesda. Maryland: May 2001.

Classification	Conventional Units (mg/dL)	SI Units (mmol/L)	Alternate Units (g/L)
Optimal	<100	<2.59	<1.00
Near to above Optimal	100-129	2.59-3.34	1.00-1.29
Borderline High	130-159	3.36-4.11	1.30-1.59
High	160-189	4.14-4.89	1.60-1.89
Very High	>190	>4.91	>1.90

N. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.